REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Introductory Remarks

Upon entry of the foregoing amendments, claims 1, 15, 28, 31-35, 52-54 and 56-63 will be pending in the application. Claims 1, 31, 33-34, and 52-54 are being amended. Claims 56-63 are being added. Claims 19, 24, 29-30, 36-39, 41-47, 49-51 and 55 are being canceled.

The following table identifies exemplary support for the amendments to each claim.

Claim(s)	Exemplary Support
1, 52-53	Page 37, line 1 – page 38, line 5; page 7, ll. 28-32; page 10, line 24 – page 11, line 6
31, 34, 54	Page 37, line 1 – page 38, line 5
33	Page 34, line 37 – page 38, line 5
56-63	Page 35, table 1; page 36, line 28-29; page 37, line 20 – page 38, line 5

II. The Claims Are Definite

Claims 52-55 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, it was asserted that the limitation "said disorder" in claim 52 lacked sufficient antecedent basis.

In view of the amendments to claim 52, the rejection is now moot. Claim 52 relates to a method of treating onychomycosis or tinea unguium, and where the claim formerly referred to "said disorder . . ." it now refers to "said onychomycosis or tinea unguium."

III. The Claims Are Enabled

Claims 1, 15, 19, 24, 28-39, 41-47 and 49-55 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. Although the Office acknowledged that the specification enables methods of treating onychomycosis (nail fungus) with 5-aminolevulinic acid (5-ALA), it stated that "methods of treating all fungal diseases including onychomycosis

with any agent which is not in itself a photosensitizer but which induces accumulation of protoporphyrin IX" is not enabled. Applicants respectfully traverse the rejection.

a. Precursors of Protoporphyrin IX

Without acquiescing in the propriety of the rejection, and solely to clarify the scope and interpretation of the claims, Applicants have amended the claims to recite that the administered compound is "a precursor of protoporphyrin IX."

Those skilled in the art would understand that "a precursor of protoporphyrin IX" is a compound in the heme biosynthetic pathway or a compound that would induce synthesis of protoporphyrin IX, *i.e.*, a compound that is converted *in vivo* to a compound in the heme biosynthetic pathway and therefore induces synthesis of protoporphyrin IX. For an illustration of the heme biosynthetic pathway, Applicants refer the Examiner to McGilvery et al., Biochemistry: A Fundamental Approach 632-635 (2d ed. 1979) (Exhibit 1). This textbook shows the heme biosynthetic pathway and illustrates the role of 5-aminolevulinate. The phrase "precursor of protoporphyrin IX" encompasses those items that are involved in the biosynthetic pathway of heme as shown in McGilvery.

Additionally, the present specification discloses at the paragraph bridging pages 10-11 that "the usual rate-limiting step in the [heme biosynthetic] process, the synthesis of 5-aminolevulinic acid, can be bypassed by the provision of exogenous ALA, porphobilinogen or other precursor of PpIX."[1] Those ordinarily skilled in the art would understand an "other precursor" of protoporphyrin IX to include prodrugs of compounds in the heme biosynthetic pathway. Such an "other precursor" would include, for example, an ester of 5-aminolevulinic acid. To support this position, Applicants offer, De Matties et al., "Brain 5-aminolaevulinate synthase," Biochemical Journal, vol. 196, 811-817 (1981) (Exhibit 2). De Matties et al. disclose that ". . . the methyl ester [of 5-aminolevulinic acid] reflects passive diffusion of the unchanged methyl ester across the blood/brain barrier, followed by hydrolysis to the free amino acid within the brain and subsequent conversion of 5-aminolaevulinate into haem." This reflects knowledge at the time of the invention that an agent such as an ester of 5-

[1] This language is present in each parent application/patent to which the present application claims priority.

aminolevulinic acid could be administered to a patient to achieve conversion into heme and, accordingly, synthesis of protoporphyrin IX (a precursor to heme).

Also, Applicants submit Srivastava et al., "Regulation of 5-Aminolevulinate Synthase mRNA in Different Rat Tissue," Journal of Biological Chemistry, vol. 263, 5202-5209 (1988) (Exhibit 3) to further support the knowledge at the time of the invention that an ester of 5-aminolevulinic acid, such as the methyl ester, was known to enter the heme biosynthetic pathway via 5-aminolevulinic acid and therefore is active in inducing synthesis of protoporphyrin IX (a precursor to heme). Srivastava et al. disclose that "[a]dministration of hemin to rats reduced the basal level of this mRNA [a specific 5-aminolevulinate synthase] only in liver, but the heme precursor, 5-aminolevulinate (or its methyl ester) repressed the basal levels in liver, kidney, heart, testis and brain."

Thus, at the time of the invention, the phrase, "a precursor of protoporphyrin IX" included substances such as 5-aminolevulinic acid as described in the present specification, the shown and listed precursors of PpIX as described by McGilvery in Biochemistry and esters of 5-aminolevulinic acid, such as the methyl ester of 5-aminolevulinic acid as described by Srivastava et al. and De Matties et al.

b. Methods of Treating Fungal Infections Affecting the Skin or Nails

The amended claims are directed to methods of treating fungal infections affecting the skin or nails, and not *any* fungal disease. Claims 31-32 and 52-54 are particularly directed to treating onychomycosis or tinea unguium. Example 9 in the specification recounts a successful application of the invention for treating nail fungus, and constitutes strong evidence that the claimed invention is enabled. That example specifically demonstrates that fungi affecting the integumentary system are capable of taking up protoporphyrin IX precursors and processing those precursors to make a photoactive compound. It further demonstrates that subsequent exposure of the fungi to a photoactivating spectrum of light kills the fungi. Thus, Example 9 correlates with and supports enablement of the full scope of the claimed invention.

In view of the foregoing amendments and comments, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

IV. The Claims are Non-Obvious

Claims 1, 15, 19, 24, 28-39, 41-47 and 49-55 were rejected under 35 U.S.C. § 103 as allegedly being obvious over Levy (U.S. Patent No. 5,283,255) and Richter (U.S. Patent No. 5,705,518). Applicants respectfully traverse the rejection.

a. The Office's Rationale

The Office relies on Levy to teach that photosensitizing agents such as hydromonobenzoporphyrins can be used in photodynamic therapy for the treatment of athlete's foot and fungal diseases in general. However, Levy does not teach the use of 5-aminolevulinic acid (5-ALA), a precursor to protoporphyrin IX. The Office relies on Richter to teach that photosensitizing agents such as the porphyrins provide the same effect as 5-ALA. Therefore, the Office concludes that it would have been obvious to use 5-ALA in the method of Levy, which is directed to treating athlete's foot, which is caused by the same fungus as the fungus which causes onychomycosis.

b. The Cited References Did Not Teach or Suggest the Claimed Invention

For an invention to be obvious, the prior art must have taught or suggested the invention, but such was not the case for the presently claimed invention.

The cited references neither teach nor suggest that fungi are capable of taking up a protoporphyrin IX precursor and converting it to protoporphyrin IX. The benzoporphyrin compounds that Levy allegedly recommended for treating athletes foot are themselves photoactive, and therefore do not require conversion after being taken up by fungi. Levy is silent about whether fungi will convert a precursor into protoporphyrin IX. Richter also is silent on this issue, as that reference is limited to directing photodynamic therapy at *animal* tissues and *animal* cells.

c. *No Likelihood of Success Previously Existed for Using Precursors of Protoporphyrin IX in Photodynamic Therapy to Treat Fungal Infections*

Obviousness also requires a reasonable likelihood of success for practicing the invention, but such a likelihood did not previously exist for the presently claimed invention.

Even if Levy and Richter did suggest trying the claimed invention (which they did not), those references did not provide a reasonable expectation for *successfully* practicing the

invention. The biology of fungi and animals are significantly different, such that one could not predict whether fungi, like animal cells, would take up a protoporphyrin IX precursor and convert it to protoporphyrin IX.

With regard to claims 31-32 and 52-54, which are directed to treating nail infections, the likelihood of success was still lower because nail infections are notoriously difficult to treat. *See,* Campbell et al., stating, "[o]nychomycosis is a common nail disease responsible for approximately 50% of disease of the nail . . . the diagnosis and treatments are difficult and the choice of appropriate antifungal drugs complex and require the knowledge of the chemical structures of the metabolites of the molds that cause onychomycosis and their interaction with the antifungal drugs" (Abstract, Scientific World Journal, 2004 Aug 31; 4; 760-777) (already of record). *See, also* Gupta et al. stating, "[o]nychomycosis is a fungal infection affecting the nail bed and nail plate; it may be chronic and can be difficult to treat" (Abstract, Am. J. Clin. Dermatol. 2004; 5(4); 225-37) (already of record). In addition, Albert et al. recognize the difficulty in treating onychomycosis, where they state, "[o]f all superficial fungal infections, onychomycosis is the most difficult to manage. Practitioners of all disciplines realize its chronic nature, difficulty in eradication and propensity to recur" (Abstract, Clin. Podiatr. Med. Surg. 2004 Oct. 21(4); 605-15) (already of record). Omero et al. support this proposition, "[o]nychomycosis--the dermatophytic invasion of the nail--is difficult to eradicate with drug treatment" (Abstract, Mycopathologia, 2004 Aug; 158(2): 173-80) (already of record).

Each of the references cited above was published in 2004, several years after the present application was filed. Since the level of skill in the art is ever expanding and not contracting, the references establish that at the time of Applicants' filing, one skilled in the art would have understood that treating onychomycosis is quite difficult.

Only recently have studies been performed directed to the use of photodynamic therapy for treatment of the dermatophyte Trichophyton, one of the fungi which can cause onychomycosis.[2] Smijs et al. disclose using porphyrins for photodynamic killing of the

[2] The primary fungi that cause onychomycosis are trichophyton rubrum and trichophyton mentagrophytes. They are dermatophytes (fungi that infect hair, skin, and nails) and feed on keratinized (nail) tissue. The infections they cause are normally confined to the nails, but

dermatophyte. In fact, Smijs states, "[t]he present study shows that Trichophyton rubrum in suspension culture is susceptible to photodynamic treatment, a completely new application in this area." (Photochem. Photobiol 2003 May; 77(5); 556-60, abstract) (already of record). In a later publication also by Smijs, he states, "[t]he application to photosensitizers for the treatment of fungal infections is a new and promising development within the field of photodynamic therapy." (Photochem. Photobiol 2004 Sep-Oct; 80(2): 197-202, abstract) (already of record).

Given the uncertainty about whether fungi would process a protoporphyrin IX precursor and the notorious difficulty of treating nail fungus at the time this application was filed, the Examiner's interpretation of Levy and Richer to establish that the claimed invention is *prima facie* obvious is improper and based on hindsight knowledge. Accordingly, Applicants respectfully request withdrawal of the obviousness rejection.

V. Concluding Comments

This application is now in condition for allowance, and favorable reconsideration of it is respectfully requested.

If the Examiner believes that an interview would further advance prosecution of the application, he or she is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

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occasionally spread to the surrounding skin. Another type of onychomycosis is caused by yeast (candida albicans or candida parapsilosis). These infections are less common but produce similar symptoms. See http://www.podiatrychannel.com/onychomycosis

Respectfully submitted,

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